RESEARCH ARTICLE

Clinical Features and Survival Analysis of Very Young (Age<35) Breast Cancer Patients

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Abstract

Objectives: To compare the clinicalpathological features and prognosis between premenopausal breast cancer patients aged of <35 and ≥35 years old. Methods: The clinical data and survival status of 1498 cases premenopausal operable breast cancer treated in our hospital from 2002.1 to 2004. 12 were collected, 118 cases were aged <35. They were divided into 4 groups: Luminal A, Luminal B, HER2-positive, Triple-negative. The disease free survival (DFS) and overall survival (OS) were identified. Results: The 5-year DFS and OS rates were significantly lower in age<35 than in age≥35 patients. In the Luminal B, HER2-positive, Triple-negative group, the 5-year recurrence risk was higher in age<35 than in age≥35 patients, and age<35 patients' 5-year death risk was higher only in Luminal B, Triple-negative group. Regardless of whether lymph node involved, age<35 patients had a bad prognosis in both DFS and OS. Conclusions: Compared with premenopausal age ≥35 breast cancer, age<35 patients had a worse outcome.

Keywords: Breast neoplasms - very young patients - prognosis

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Introduction

There are still controversies about the definition of "very young age". International multicenter clinical trials considered 35 years as the age boundary (Lilla Madaras et al., 2013). Breast cancer is uncommon in very young women (<35 years old), only accounting for fewer than 4% in Western countries(Winchester, 1996; Chung et al., 1996). But in Asian, the morbidity rate is up to 9.5%~12%(Han W et al., 2004), more higher than Western countries. In China, the proportion of patients in this age group was reported to 10%~15% (Meng et al., 2007).

Until now whether age is an independent prognostic factor remains a controversy with few well-designed studies investigating this group of women. But the limit results still show that very young breast cancer patients (age<35 years) have worse outcomes compared with less young premenopausal patients (age ≥35 years).

In this study, we retrospectively investigated the general features, clinicopathological features, treatments and outcomes obtained in 1498 premenopausal operable patients followed at our hospital with the diagnosis of breast cancer between 2002 and 2004.

Materials and Methods

We collected information of 1498 cases operated from 2002 to 2004 at Cancer Institute and Hospital of Tianjin Medical University. Pathological assessment included evaluation of the primary tumor size, histological type and lymph nodes status. Tumor stage was based on the 6th American Joint Committee on Cancer (AJCC) criteria. Histological type and grading followed the World Health Organization (WHO) classification. ER, PR and HER-2 overexpression were evaluated immunocytochemically. The threshold for ER and PR positivity was 10%. For HER-2 assessment, tumor were scored according to the intensity and completeness of cell membrane staining, in a 4-tier scale (0: no immunoreactivity, 1+: weak and incomplete membrane staining, 2+: weak/moderate and complete membrane staining, 3+: strong and complete membrane staining). Tumor scored 3+ were considered as overexpressing HER2. Immunohistochemical classification as follows: Luminal A: (ER+ or PR+) and (HER-2 0/+/++); Luminal B: (ER+ or PR+) and (HER-2 +++); HER-2 positive: (ER- and PR-) and (HER-2 +++) and Triple negative: (ER- and PR-) and (HER-2 0/+/++). The Mantel-Haenszel chi-square test for trend was used to assess the association between, respectively, categorical and ordinal variables. The end points were the incidence of disease-free survival (DFS) and overall survival (OS). DFS was defined as the length of time from the date of surgery to any tumor related relapse. OS was determined as the time from surgery until the date of death or the date

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Table 1. Comparison of Clinical Features Between Very Young and Less Young Breast Cancer [n(%)]

Characteristics	Age<35 (n=118)	Age≥35 (n=1380)	χ^2	*P* value
Stage				
0+I+II	74(62.7%)	1068(77.4%)	12.929	0.000**
III	44(37.3%)	312(22.6%)		
Histology				
Ductal carcinoma	99(83.9%)	1158(83.9%)	0	0.997
Others	19(16.1%)	222(16.1%)		
Tumor size				
≤5 cm	105(89.0%)	1307(94.7%)	6.589	0.010*
>5 cm	13(11.0%)	73(5.3%)		
Tumor grade				
G1	6(5.1%)	48(3.5%)	1.27	0.736
G2	77(65.3%)	948(68.7%)		
G3	16(13.6%)	162(11.7%)		
Unknown	19(16.1%)	222(16.1%)		
Number of positive nodes				
None	52(44.1%)	722(52.3%)	2.964	0.085
Yes	66(55.9%)	658(47.7%)		
ER				
Positive	47(39.8%)	712(51.8%)	6.018	0.014*
Negative	71(60.2%)	668(48.2%)		
PR				
Positive	46(39.0%)	702(50.9%)	6.144	0.013*
Negative	72(61.0%)	678(49.1%)		
HER-2				
Positive	58(49.2%)	451(32.7%)	13.147	0.000**
Negative	60(50.8%)	929(67.3%)		
Molecular classification				
Luminal A	28(23.7%)	652(47.2%)	26.057	0.000**
Luminal B	32(27.1%)	216(15.7%)		
HER-2 positive	26(22.0%)	235(17.0%)		
Triple negative	32(27.1%)	277(20.1%)		
Surgery				
BCS	20(12.7%)	132(10.1%)	5.345	0.021*
Mastectomy	98(87.3%)	1176(89.9%)		
Chemotherapy				
Yes	110(93.2%)	1232(94.2%)	0.183	0.668
No	8(6.8%)	76(5.8%)		
Hormone therapy				
Yes	60(50.8%)	859(62.2%)	5.957	0.015*
No	58(49.2%)	521(37.8%)		

*P<0.05; **P<0.001; ER, estrogen receptor; PR, progesterone receptor; BCS, breast conservation surgery

of last follow-up. Cumulative incidence and survival plots according to age were drawn using the Kaplan-Meier method. The log-rank test was used to assess survival difference between strata. Cox regression was applied for Hazard Ratio (HR) and 95% Confidence Interval (CI) in subgroups. Statistical significance was considered at P<0.05. All analyses were carried out with the SPSS16.0 software.

Results

A total of 1498 premenopausal patients diagnosed as breast carcinoma from 2002 to 2004, and a total of 118 (7.9%)cases belonged to the very young group (age<35 years) and 1380 (92.1%)cases belonged to the less young group (age≥35 years). The characteristics of the assessable patients are given in Table 1.

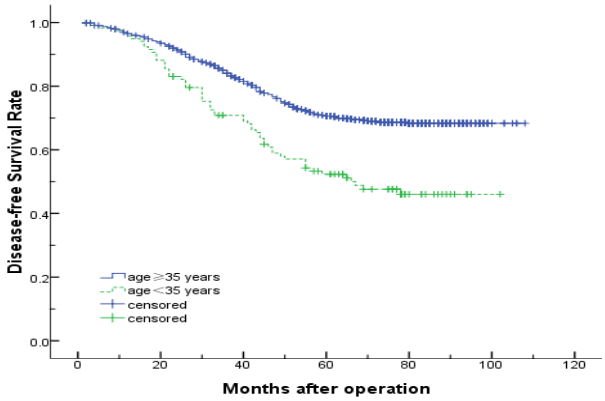

Figure 1. Comparison of DFS Between Very Young (age < 35 years) and Less Young (age ≥ 35 years) Breast Cancer (*P*=0.000)

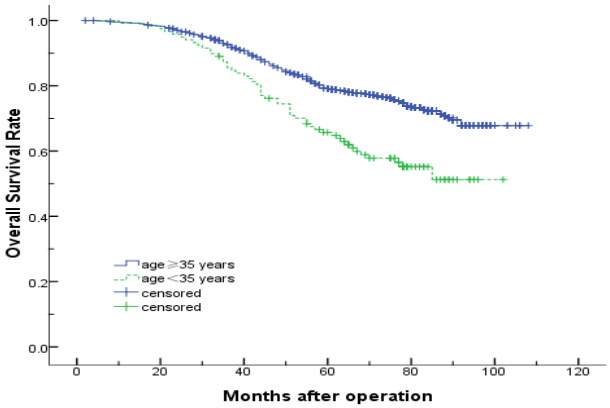

Figure 2. Comparison of OS Between Very Young (age < 35 years) and Less Young (age ≥ 35 years) Breast Cancer (*P*=0.000)

The group of very young patients (age<35 years) had more tumors classified as stage III (37.3% vs 22.6%), larger tumor size (11.0% vs 5.3%) than less young patients (both P<0.05). They also had significant lower ER (39.8% vs 51.8%, P=0.015), lower PR (39.0% vs 50.9%, P=0.015) and higher HER-2 (49.2% vs 32.7%, P=0.000) expression. Mastectomy and endocrine therapy rate was higher in less young patients group, and the difference was significant (both P<0.05).

The median follow up was 67.42 months. The 5-year disease free survival rate was 52.3% for very young patients and 70.9% for less young patients (P=0.000). The 5-year overall survival rate was 65.7% for very young patients and 79.3% for less young patients (P=0.000). (Figure 1, 2)

When we analyzed the subtypes according to molecular classification, very young group showed worse outcomes than less young group. Very young patients with tumors classified as Luminal B, HER2 and Triple Negative were at increased risk of poor DFS (HR=1.741, 95%CI 1.059- 2.863; HR=1.793, 95%CI 1.072- 3.001; HR=1.804, 95%CI 1.078- 3.019, respectively).While in the Luminal B and Triple Negative subtypes, patients <35 years had a higher risk of death (HR=2.628, 95%CI 1.464-4.717; HR=1.866, 95%CI 1.051-3.312, respectively) (Figure 3). When we analyzed the subtypes according to node involvement, we concluded that regardless of node status, very young patients were at increased risk of poor DFS

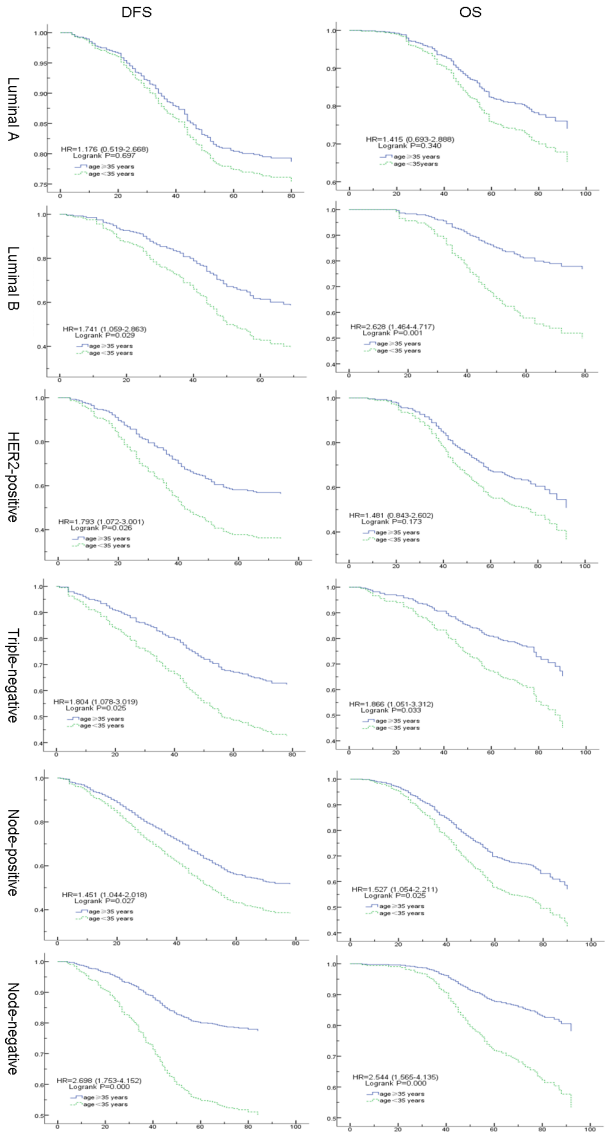

Figure 3. COX's Proportional Hazard Regression Models for DFS and OS in Subtypes

and OS. Particularly in node-negative group, patients <35 years had a twofold higher risk of death compared with older patients (HRDFS=2.711, 95%CI 1.761-4.172; HROS=2.556, 95%CI 1.572-4.155) (Figure 3).

Discussion

Consensus has been reached that breast cancer in very young age is different from less young age. Young patients often show more aggressive biologic behavior, such as advanced stage, less ER positive expression, higher histological grade and more peritumoral vascular invasion (Gajdos et al., 2000;Vrieling et al., 2003; Kim et al., 2007).

Our study showed that in the group of very young patients (age <35 years), there were more Triple Negative tumors than older patients. Many researches demonstrated that a relationship exists between age and the proportion of breast cancer subtypes. Bauer et al.' (2007) research showed that patients with the Triple Negative subtype were likely to be under the age of 40 years.

Gajdos et al. (2000) conducted a study from 1989 to 1997 in New York, and found that very young (age ≤35 years) patients more frequently presented tumors with large tumor size, advanced stage and node positive. While in our study stageIII and size >5cm tumors were more frequently in very young patients (age < 35 years). And there were statistical significance between very young and less young groups, which was accordance with literatures (Kim et al., 2007). The node positive proportion was higher in age<35 years patients than age≥35 years patients (55.9% vs 47.8%, respectively), but did not differ significantly (P=0.088).

Our research, same as other researches (Ahn et al., 2007), showed more extensive ER negativity, PR negativity and HER2 positivity in very young patients than less young patients (60.2% vs 48.2%, P=0.015). Maybe it accounted for poor effect of endocrine therapy. Several literatures had shown a crosstalk between ER and growth factor receptor pathways, which had been considered as a cause for endocrine therapy resistance in breast cancer (Osborne et al., 2005). Very young patients tended to be more HER2 over-expression, and the difference was significant for less young patients (49.2% vs 32.5%, P=0.000). Therefore, we might assume that HER2 over-expression is the risk factor of poor prognosis. That was in accordance with some literatures (Cancello et al., 2010), but others showed that there was no difference between two groups (Colleoni et al., 2002). So other large multi-institution analysis is required to conform that HER2 is an independent prognosis factors for very young patients.

When we compared the adjuvant treatment, we found that very young patients tended to have breast conservation surgery than less young patients (12.7% vs 10.1%, P=0.021). This was no conclusion whether age was a risk factor for local recurrence of breast cancer. Several clinical trials showed that very young patients had a higher risk of local recurrence. But because of few sample of our study, we did not have a further research. It is reported that the survival of breast cancer is related to hormonal receptors expression. Hormone receptor positivity has been regarded as predictive of better prognosis in breast cancer patients. We found that very young patients had less ER/PR expression and hormonal treatment than did their older counterparts. This is supported by other results that very young patients with hormone receptor-positivive tumors had a worse outcome than less young patients.

Univariate analysis show age<35 years and age≥35 years patients have significant difference in DFS (49.5% vs 68.9%) and OS (65.7% vs 79.4%), both p <0.05. Similar tendency could be seen in other studies. Kothari et al. (2002) compared the prognosis of age<35 years and age≥35 years patients, the former survival rate remarkably lower than the later.

We found that in Luminal A subtype, the two age groups recurrence and death risk had no difference. But in Luminal B subtype, both recurrence and death risk in age<35 years group was higher than age≥35 years group. This indicated that HER2 overexpression might be an important factor to prognosis, so patients might benefit from target therapy about HER2. Whether age is an important factor for prognosis in node negative patients has not unified yet. In some European and American

countries (Muscolino et al., 1987; Schmidt et al., 1991), experts think that very young patients with node positive, DFS and OS are shorter than less young patients. But there are no differences in node negative patients. Consensus at the St Gallen (Goldhirsch et al., 1998; Goldhirsch et al., 2001) conferences of 1998 and 2001 indicated that age<35 years was a risk factor for recurrence in node negative breast cancer. And our results was that no matter whether node invasive, age<35 years patients' DFS and OS was lower than age≥35 years patients, especially in node negative subtype, both the recurrence and death risk of age<35 years patients were twice as age≥35 years patients.

Our study also has some limitations. Firstly, there were no immunohistochemical results of ER, PR and HER2 for a little portion of patients. Some patients could not be contacted and their survival status could not be included in the analysis. As a result, datum cannot be 100% completeness. Secondly, since young breast cancer cases are relatively less, there is no difference on DFS and OS in Luminal A subtype. If we could enlarge the sample, or divide into more groups, we might get some significant results. Thirdly, some cases had a short-term follow-up. If it could be prolonged, we could further analyze the relations between recurrence rate and time. Lastly, young breast cancer tended to be more BRCA1 and BRCA2 mutations (FitzGerald et al., 1996; Robson et al., 1998). But our patients had no genetic testing. If we could investigate this character, we could understand more about very young breast cancer.

In conclusion, compared with less young breast cancer, very young patients have advanced clinical stage, large tumor, lower ER expression, higher HER2 overexpession and shorter 5-years DFS and OS. Divided by the molecular classification and lymph node involvement, two age groups had different recurrence and death risks. Very young patients with node-negative had more apparently different prognosis from less young patients, so we should pay more attentions. Our focus in the future is looking for more effective treatments and further division of breast cancer subtypes. According to their characteristics relatively, we could formulate concrete, effective and personalized treatments.

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